REMARKS

Reconsideration and withdrawal of the rejections of the claims, in view of the amendments and remarks herein, is respectfully requested. Claims 1, 2, 10, and 20 are amended, claim 24 is canceled, and claims 46-47 are added. The amendments are intended to advance the application and are not intended to concede to the correctness of the Examiner's position or to prejudice the prosecution of the claims prior to amendment, which claims are present in a continuation of the present application. Claims 1-23 and 25-47 are pending.

New claim 46 is supported at, for instance, page 4, lines 23-24 of the specification.

New claim 47 is supported by, for example, Figure 11 of the specification.

The 35 U.S.C. § 112, Second Paragraph, Rejection

Claims 10 and 30-31 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite over optimized in "any host cell". The amendment to claim 10 obviates the § 112(2) rejection. Therefore, withdrawal of the § 112(2) rejection is respectfully requested.

The 35 U.S.C. § 112, First Paragraph, Rejection

Claims 1-11, 15-16, 18-20, 24-25, 30-32, 34-37, and 41-44 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner asserts that the specification only describes polynucleotides having the nucleic acid sequence of SEQ ID NO:72, which encodes a fusion polypeptide comprising a specific luciferase, a specific PEST sequence, and a specific CL1, and that does not constitute a representative number of species to describe polynucleotides encoding a fusion polypeptide comprising a whole genus of variants, recombinant and mutants of any or all reporter protein or luciferase and any or all protein and/or mRNA destabilization sequence or any or all PEST sequences. This rejection, as it may be maintained with respect to the pending claims, is respectfully traversed.

In response to Applicant's argument and evidence that reporter proteins, protein destabilization sequences and mRNA destabilization sequences are known in the art, the Examiner responds that the claims are not limited to only those sequences exemplified in the specification and known sequences. However, Applicant need not describe what is known to the

art. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81, 94-95 (Fed. Cir. 1986). The documents submitted with the Amendment filed on March 29, 2007, as well as the references cited against the claims under 35 U.S.C. §§ 102(b)/103(a), clearly evidence that sequences for reporter proteins, protein destabilization sequences and mRNA destabilization sequences were known to the art.

What is required to provide an adequate written description for a claimed genus, is that the specification provides a sufficient description of a representative number of species by an actual reduction to practice, reduction to drawings or by a disclosure of relevant, identifying characteristics, i.e., by a structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics (Guidelines for Examination of Patent Applications under the 35 U.S.C. § 112(1) Written Description Requirement, Fed. Reg., 66, 1099 (2001)). Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. (Fed. Reg., December 21, 1999 (Volume 64, Number 244).

The properties (attributes) that identify the genus of nucleic acid molecules are that the sequences in the nucleic acid molecules are those for a reporter protein, and a protein destabilization sequence and/or RNA destabilization sequence, or combinations thereof. Underlying each of these properties is a structure. That is, not every nucleotide sequence encodes a reporter protein; not every nucleotide sequence present in a larger nucleotide sequence, once translated to a protein, confers a decreased half-life upon the translated protein; and not every nucleotide sequence present in a larger nucleotide sequence, once transcribed, confers a decreased stability to the resulting mRNA. Moreover, the specification exemplifies three different firefly luciferase sequences, two different click beetle luciferase sequences, a *Renilla* luciferase sequence, a green fluorescent protein sequence, protein destabilization sequences (see pages 5 and page 23 which disclose numerous sources for protein destabilization sequences), and RNA destabilization sequences (see page 6 of the specification). One of skill in the art in view of Applicant's disclosure can recognize other members of "reporter protein",

"protein destabilization sequence" and "RNA destabilization sequence" in view of the species disclosed in Applicant's specification.

The Examiner is respectfully requested to consider that specification at issue in Univ. Calif. v. Eli Lilly and Co., 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997) *did not disclose a nucleotide sequence for the claimed human cDNA and disclosed only one rat cDNA sequence for the claimed vertebrate or mammalian cDNAs.* In contrast to the claims at issue in Eli Lilly, Applicant discloses numerous nucleotide sequences falling within the scope of the claimed genus.

Moreover, the Examiner is requested to consider that the terms at issue in the present application are not new or unknown biological material that the skilled artisan could easily miscomprehend. In Amgen v. Hoechst Marion Roussel, 314 F.3d 1313, 65 U.S.P.Q.2d at 1398 (Fed. Cir. 2003), the Federal Circuit pointed out that in Enzo Biochem. v. Gen-Probe, Inc., 296 F.3d at 1324, 63 U.S.P.Q.2d at 1613 (Fed. Cir. 2002), it was clarified that Eli Lilly did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure. The Federal Circuit continued stating that both Eli Lilly and Enzo Biochem. are inapposite to Amgen because the claim terms at issue ("vertebrate" and "mammalian") were not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend because they readily "convey distinguishing information concerning [their] identity" such that one of ordinary skill in the art could "visualize or recognize the identity of the members of the genus." Eli Lilly, 119 F.3d at 1567, 1568, 43 U.S.P.Q.2d at 1406. The words "reporter protein", "protein destabilization sequence" and "mRNA destabilization sequence" readily convey distinguishing information concerning their identity such that one of ordinary skill in the art can visualize or recognize the identity of the members of the genus.

Thus, withdrawal of the § 112(1) rejection is respectfully requested.

The 35 U.S.C. § 102(b) Rejection

Claims 1, 4-7, 10, 20, 25, 32, 35-37, and 41-44 were rejected under 35 U.S.C. § 102(b) as being anticipated by Corish et al. (Protein Eng., 12:1035 (1999)). This rejection, as it may be maintained with respect to the pending claims, is respectfully traversed.

Corish et al. disclose a constructs having green fluorescent protein (GFP) linked to a 27 amino acid sequence from murine ODC that contained a PEST sequence or a 116 residue fragment from cyclin B1 that contained a destruction box (CDB), or both. Notably, the presence of both sequences resulted in a protein having a half-life substantially the same as the protein with only the CDB sequence.

Corish et al. do not teach or suggest an isolated nucleic acid molecule comprising a nucleic acid sequence encoding a fusion polypeptide comprising a reporter protein and at least two different heterologous protein destabilization sequences, wherein one heterologous protein destabilization sequence is SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, or SEQ ID NO:98.

Accordingly, withdrawal of the § 102 rejection is respectfully requested.

The 35 U.S.C. § 103 Rejection

Claims 1-11, 15-20, 24-25, 30-32, 34-37, and 41-44 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Leclerc et al. (Biotechniques, 29:590 (2001)), Corish et al., Gilon et al. (EMBO J., 17:2759 (1998)) and Kastelic et al. (WO 00/36314). As this rejection may be maintained with respect to the pending claims, it is respectfully traversed.

Leclerc et al. prepared a construct in which a coding sequence for a firefly luciferase was linked to a murine ornithine decarboxylase (mODC) coding sequence that includes a PEST sequence found near the C-terminal of mODC. It is disclosed that the PEST sequence in mODC corresponds to residues 423-450, and that residues 423-461 of mODC (modified by an amino acid substitution at two positions), i.e., the C-terminal residues of mODC, were fused to firefly luciferase sequences (see Figure 1).

The Examiner acknowledges that Leclerc et al. do not teach the use of combinations of protein destabilization sequences, or a polynucleotide with at least one mRNA destabilization sequence (page 12 of the Office Action).

The Examiner asserts that one having skill in the art would have recognized the advantage to further decrease the half-life of the luciferase of Leclerc et al. by using an additional destabilizing sequence in conjunction with the PEST sequence, such as the CDB of Corish et al. or other protein destabilizing sequences known in the art, such as CL proteins, or other methods that decrease expression of proteins, in order to make a reporter protein with a short half-life of expression.

However, Corish et al. teach away from the use of combinations of protein destabilization sequences to further decrease protein half-life, as GFP with both PEST and CDB sequences had a half-life that was almost the same as GFP with only a CDB sequence, i.e., there was no significant advantage to having both protein destabilization sequences as CDB alone resulted in almost the same effect. Nor does Corish et al. teach or suggest other methods to decrease expression of proteins.

Gilon et al. do not provide what is missing in Leclerc et al. or Corish et al., as Gilon et al. do not teach or suggest the use of particular combinations of protein destabilization sequences, the use of a mRNA destabilization sequence with particular protein destabilization sequences, or a codon optimized luciferase sequence with at least one destabilization sequence.

Kastelic et al. disclose a construct having a coding region for luciferase (from pGL2) linked to a mRNA instability sequence (clone # 63) and its use in a method to screen for compounds that promote the instability of mRNAs with mRNA instability sequences. The effect of the mRNA instability sequence on luciferase expression in the results shown in Figure 4 is not particularly apparent until 24 hours after differentiation is induced, although the overall signal of clone # 63 is 3- to 5-fold less than the control clone (clone # 53, which has a luciferase construct but no mRNA instability sequence). With reference to this data, it is disclosed that one "would expect in the case of luciferase to see a weaker effect of mRNA destabilizing drugs since transcription remains high" (page 12).

Treatment of the clones with an agent known to promote the instability of mRNAs (a radicicol analog, i.e., SDZ 216-732) resulted in a decrease in activity in clone # 63 over time

(Figure 5). Treatment of the clones with actinomycin D (an agent that binds DNA at the transcription initiation complex and prevents elongation) resulted in a decrease in activity for both clones but relatively less of a reduction for clone # 63, while treatment of the clones with cycloheximide (an agent that inhibits protein synthesis) resulted in a decrease in activity clone # 53 and an increase in activity for clone # 63 (Figure 5).

If there are fewer luciferase mRNAs available for translation in clone # 63 cells as a result of the mRNA instability sequence, it is unclear why clone # 63 has more activity than clone # 53 in the presence of actinomycin D or cycloheximide at 8 hours. Moreover, the reduced activity for clone # 63 in the presence of SDZ 216-732 relative to clone # 53 at 8 hours in Figure 5 may be due to the reduced signal for clone # 63 (see Figure 4).

Kastelic et al. do not supplement what is missing in Leclerc et al., Corish et al., and Gilon et al., as Kastelic et al. do not disclose or suggest the use of particular combinations of protein destabilization sequences, the use of a mRNA destabilization sequence and a particular protein destabilization sequence, or a codon optimized luciferase sequence with at least one destabilization sequence.

The Examiner asserts that in combining the teachings of Leclerc et al., Corish et al., Gilon et al. and Kastelic et al., it would have been obvious to one having ordinary skill in the art to make a polynucleotide encoding a fusion protein comprising a firefly luciferase and one or more protein destabilization sequences, such as a PEST sequence and a CL1 sequence, and/or one or more mRNA destabilization sequence. The Examiner continues that one of ordinary skill in the art would have been motivated to use other protein destabilizing sequences such as the CL sequences of Gilon et al. or a cyclin destruction box sequence as taught by Corish et al. or one or more mRNA destabilization sequences of Kastelic et al. in conjunction with PEST sequence in order to further reduce the half life activity/expression of luciferase. The Examiner asserts that one of ordinary skill in the art would have had a reasonable expectation of success since Leclerc et al. teach reducing the half-life activity of a luciferase by using a PEST sequence, Corish et al. teach that a combination of two protein destabilization sequences decreases half-life of reporter protein more than using only one of the protein destabilizing sequences, Gilon et al. teach CL protein destabilizing sequences that can be used to destabilize proteins, and Kastelic et al. teach destabilizing reporter proteins using mRNA destabilizing sequences.

The Examiner is reminded that the Examiner has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. In re Fine, 837 F.2d 1071, 1074, 5 U.S.P.Q.3d (BNA) 1596, 1598 (Fed. Cir. 1988). The M.P.E.P. contains explicit direction to the Examiner that agrees with the court's holding in In re Fine:

> In order for the Examiner to establish a *prima facie* case of obviousness, three base criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one or ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure. M.P.E.P. § 2142 (citing In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d (BNA) 1438 (Fed. Cir. 1991)).

With respect to claims 1 and 2, the combination of the cited art does not disclose or suggest combining the recited protein destabilization sequences with a mRNA destabilization sequence or with a different protein destabilization sequence. Nor does the cited art teach or suggest a codon optimized luciferase sequence with at least one destabilization sequence. Therefore, the cited art fails to teach or suggest all the claims limitations.

Moreover, because Corish et al. did not achieve an additive effect with two protein destabilization sequences, the combination of the cited art fails to provide the motivation and the reasonable expectation of success alleged by the Examiner and, as discussed above, Corish et al. teach away from combining heterologous protein destabilization sequences. Even if, assuming for the sake of argument, one of skill in the art would be motivated by Corish et al. to combine heterologous protein destabilization sequences, Corish et al. teach a particular set and linear orientation of protein destabilization sequences (CDB-GFP-PEST).

Further, one of skill in the art would not look to combining different types of destabilization sequences. First, the purpose of the two types of destabilization sequences is different. As transcription preceeds RNA processing and RNA processing preceeds translation, a mRNA instability sequence decreases the amount of translatable mRNA, which in turn decreases the amount of translated protein, but the half-life of the translated protein is unaltered. For constructs with a mRNA destabilization sequence, this allows for screening of agents that promote mRNA destabilization. The presence of a protein destabilization sequence in a

translated protein targets the protein for more rapid degradation than a corresponding protein without the protein destabilization sequence. A construct with a protein destabilization sequence would not be useful in screening for agents that promote mRNA destabilization.

And although the half-life of luciferase was significantly decreased by the addition of a PEST sequence, the overall signal was likewise reduced (see Figure 2 in Leclerc et al., which shows that at 30 minutes the signal was reduced to about 10% that of the control). Similarly, the signal for a construct with a mRNA destabilization sequence was 3- to 5- fold less than a construct without the mRNA destabilization sequence (Kastelic et al.). Thus, prior to Applicant's disclosure, one of skill in the art would not consider combining two different types of destabilization sequences with a reporter gene, as the reduction in available reporter protein mRNA transcripts that can be translated in conjunction with a reduction in reporter protein half-life may not yield sufficient reporter protein for any particular assay.

Moreover, prior to Applicant's disclosure, it was unknown whether different types of destabilization sequences would have complementing or additive effects, or whether different destabilization sequences would have similar properties when combined with different reporters.

In this regard, please consider that a protein destabilization sequence had relatively little impact on a click beetle luciferase (Figure 16 in Applicant's specification). Moreover, the relative luminescence of a *Renilla* luciferase-PEST-RNA destabilization sequence construct was significantly reduced compared to a *Renilla* luciferase-PEST construct (Figure 9C in Applicant's specification). Further, the rapid and/or significantly larger increase in induction of expression in a luciferase-CL-PEST construct and luciferase-CL-PEST-RNA destabilization sequence constructs, relative to a luciferase-PEST construct, was unexpected (see Figures 10B, 15 and 16).

Thus, withdrawal of the § 103 rejection is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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Dawn M. Poole

Name

Signature